IV. Remarks

Applicants extend their thanks to the Examiner for his explanation of the rejections. Applicants have responded accordingly and believe the application is in a condition for allowance.

a. Rejection of Claims 4, 6, 10, 12, and 16

Applicants have amended the Claims to state change the term modify to inhibit. Applicants expressly reserve the right to pursue stimulation in a subsequent application. The amendment is believed to overcome all 35 USC §112, 1st ¶ rejections. Accordingly, Applicants respectfully request reconsideration of the rejection.

b. Rejection of Claims 4, 6, 10, 12, and 16

The Examiner has rejected the Claims as being enabled for only RA. Applicants respectfully request reconsideration in light of this response. Applicants have attached the Declaration of Dr. Andrea van Elsas, Ph.D, in support of the enablement of the present invention. Applicants have also included copies of all the references cited by Dr. Elsas.

First, the Examiner contends that the use of the term modulating the reactivity of lymphocytes can be either stimulatory or inhibitory. Applicants have amended the Claims to specify that modulating is meant as inhibition. Accordingly, Applicants respectfully request reconsideration of the rejection. Rather than the term "modulating," the term "inhibiting" is used.

Further, the Examiner contends that the Claims are limited to treatment of Rheumatoid Arthritis (RA). Applicants have submitted the Declaration as rebuttal. Paragraphs 5-8 of the Declaration explains that RA is believed to be an (auto)immune disease in which immunological tolerance to components resident in articular joints may be broken. RA is characterized by a chronic inflammatory infiltration of the synovial membrane which is associated with destruction of cartilage and bone.

Applicants assert that the evidence indicates that expression of HC gp-39 is related to monocyte to macrophage maturation. In contrast to many other monocyte/macrophage markers, its expression is absent in normal monocytes and strongly induced during late stages of human macrophage differentiation. Other cell types that express HC gp-39 include chondrocytes and synovial cells and neutrophils, the latter celltype, like macrophages, being heavily involved in inflammatory processes. As a reflection of the involvement of HC gp-39 producing cells in immune disease conditions, raised Human Cartilage glycoprotein-39 plasma levels have been detected in patients with rheumatoid arthritis, and in patients with other inflammatory conditions like osteoarthritis (OA), systemic lupus erythemathosus (SLE), and inflammatory bowel disease (IBD). Furthermore, strong expression of HC gp-39 has been detected in lesion macrophages of atherosclerosis specimens. In summary, there is ample evidence for the expression of HC gp-39 in multiple (auto)immune conditions and it is clear that tissues that contain monocytes that mature to macrophages and/or neutrophilic granulocytes do contain HC gp-39 protein. Thus, cross-tolerance with HC gp-39 resulting in the activation or reactivation of modulatory or regulatory T cells is expected to exert immune regulation

in all conditions in which cells of the monocyte/macrophage lineage, or neutrophilic granulocytes are present within the inflammatory lesion.

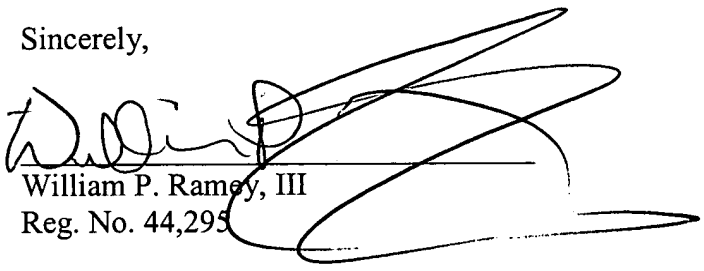
Such conditions include, but are not limited to, diseases like Graves' disease, primary glomerulonephritis, osteoarthritis, juvenile arthritis, Sjögren's disease, myasthenia gravis, rheumatoid arthritis, Addison's disease, primary biliary sclerosis, uveitis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis or diabetes. For instance, data have shown that there is a relative overexpression of macrophage-derived cytokines in orbital adipose tissue from patients with Graves' ophthalmopathy, implicating an important role for macrophages in the inflammatory lesion in this disease. Macrophages, their activation products and the regulation of cell survival (e.g. through apoptosis) play an important role in glomerulonephritis, osteoarthritis, juvenile idiopathic arthritis, Sjögrens disease, myastenia gravis, rheumatoid arthritis, liver cirrhosis, uveitis systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis or diabetes. These data exemplify the fact that cells of the monocyte/macrophage lineage play a central role in (auto)immune conditions in general. Based on the principle that HC gp-39 is expressed by macrophages on their way to full maturation, in combination with the fact that HC gp-39 induces the activation or reactivation of modulatory or regulatory cells at the site of inflammation, implies that HC gp-39 based immune intervention can be used in any (auto) immune condition. This intervention can be performed with the use of HC gp-39 protein containing a number of epitopes recognized by the immune system, or with the use of one or more selected peptides recognized by the immune system in various autoimmune conditions. Accordingly, one of ordinary skill in the art would appreciate that any autoimmune

disease could be treated with the administration of a pharmaceutical composition comprising an effective amount of HC gp-39 or fragments thereof. Therefore, Applicants respectfully request reconsideration in light of this response.

V. Conclusion

Applicants respectfully request reconsideration of the rejections in light of this response. The application is believed in a condition for allowance and Applicants respectfully request such action. Applicants respectfully request the examiner contact the undersigned attorney for an interview to expedite prosecution of the case. Please charge deposit account number 02-2334 for any required fees and to credit any credits. Further, Applicants hereby petition for a one month extension of time, the fee for which may be charged to deposit account 02-2334.

Sincerely,



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